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Article

Safety assessment of essential medicines for elderly people: a bibliographic survey

Fabiana Rossi Varallo, Fernanda Mariana de Oliveira, Patrícia de Carvalho Mastroianni*

[1]*School of Pharmaceutical Sciences, University of State of São Paulo "Júlio de Mesquita Filho", Araraquara, SP, Brazil,*

Certain medicines are considered potentially inappropriate (PIM) for elderly people as they increase the risk of adverse drug events (ADE) and because safer alternative therapies are available on the market. In this context, in order to identify the instruments that assess the quality of medical prescriptions for elderly and to determine which drugs are considered PIM, a bibliographic survey was conducted in PUBMED, LILACS and PAHO databases, in February and March/2010. The search strategy included the use of health descriptors and a manual search in the references cited by selected papers. During the period of data collection, 15 instruments were identified. In 2012, with the publication of the update of Beers criteria, this instrument was included in the study. We identified 163 PIM of 25 therapeutic classes, of which 125 (76.7%) are marketed in Brazil. Of these, 31 (24.8%) are essential medicines (RENAME 2012), of which 13 have safer therapeutic equivalents and 19 (15.2%) are over-the-counter drugs. Data suggest the need for inclusion of safer alternatives for the elderly in the national list of essential medicines and the pharmaceutical care for early detection of ADE in this age group, in order to contribute to the safe use of medicines.

Uniterms: Aged/medicines prescription. Medication/errors. Medicines/inappropriate prescribing. Medicines/adverse effects/control. Medicines/safety use. Medication/risk assessment/control. Pharmaceutical care.

Determinados medicamentos são considerados potencialmente inapropriados (MPI) para idosos, por aumentarem o risco de ocorrência de eventos adversos a medicamentos (EAM) e por existirem alternativas terapêuticas mais seguras. Neste contexto, com o intuito de identificar os instrumentos que avaliam a qualidade das prescrições médicas para idosos e verificar quais medicamentos são considerados MPI, levantamento bibliográfico foi realizado nas bases de dados PUBMED, LILACS e PAHO em fevereiro e março de 2010. Para a seleção dos manuscritos utilizaram-se descritores em saúde e busca manual nas referências bibliográficas dos artigos identificados. No período da coleta de dados, foram identificados 15 instrumentos. Em 2012, com a publicação da atualização da lista de Beers, este instrumento foi incluído no estudo. Foram identificados 163 MPI de 25 classes terapêuticas, dos quais 125 (76,7%) são comercializados no Brasil. Destes, 31 (24,8%) são medicamentos essenciais (RENAME 2012), sendo que para 13 deles há equivalentes terapêuticos mais seguros e 19 (15,2%) são medicamentos isentos de prescrição. Os dados sugerem a necessidade de inclusão de medicamentos mais seguros para idosos na lista nacional de medicamentos essenciais e do monitoramento farmacoterapêutico para a detecção precoce de EAM nesta faixa etária para contribuir com o uso seguro de medicamentos.

Unitermos: Idoso/prescrição de medicamentos. Medicação/erros. Medicamentos/prescrição inadequada. Medicamentos/efeitos adversos/controle. Medicamentos/uso seguro. Medicação de risco/controle. Monitoramento farmacoterapêutico.

C**orrespondence:** P. C. Mastroianni. Faculdade de Ciências Farmacêuticas, Universidade Estadual Paulista "Júlio de Mesquita Filho". Rodovia Araraquara - Jaú, km 1, 14801-902 - Araraquara - SP, Brasil. E-mail: pmastro@fcfar.unesp.br

INTRODUCTION

Population aging is a worldwide phenomenon. However, this process is occurring evenly over all countries. In 2050, 80% of all elderly people will be distributed among the developing nations (WHO, 2004). Thus, the United Nations Initiative (UNS, 1999) suggested that all countries should prepare their health care systems, as well as economic planning and social services in order to meet the needs of the elderly population.

In particular, the development of public health policies have to be developed for the elderly, in order to provide them with quality health care. In Brazil, the main laws are: the National Health Policy for the Elderly (Brasil, 1994), which aims "to promote healthy aging, with maintenance and improvement of their health condition, [...] functional capacity, and the prevention of disease and restoration of the health"; the Statute of Elderly People (Brasil, 2003), which ensures the comprehensive health care for the elderly, provided by the National Health Service (SUS), ensuring universal and equal access in an integrated and continuous set of actions and services for the prevention, promotion, protection and restoration of health.

Brazil is in a process of demographic transition, in which a marked aging of the population is evident. According to IBGE (2013), 33.7% of population will be more than 60 years old by 2060. Consequently, there is also an epidemiological transition, with important changes in the morbidity and mortality rates (IBGE, 2009), since the country will have changed the mortality profile until recently typical of young citizens, for a profile characteristic of senescence, with more complex and costly diseases (Gordilho *et al.*, 2000).

Elderly patients who have complex medical problems and use polypharmacy (taking five or more drugs) are particularly more likely to be affected by medication errors (Fiolavá, Onder, 2009), such as the prescription of potentially inappropriate medications (PIM), and to be hospitalized (De Paula *et al.*, 2012). Moreover, the inherent physiological changes of the aging process may influence the pharmacokinetics and pharmacodynamics of a drug, resulting in greater sensitivity to both its therapeutic and adverse effects (Corsonello *et al.*, 2010).

PIM are those medications or classes of medication that should be avoided in patients aged ≥ 65 years, since they have no clear evidence-based efficacy, are not cost-effective (Beers *et al.*, 1991) and on pose unnecessary risk to the health of the elderly, in that the risks of using those drugs exceed the benefits and safer alternatives are available (Fick *et al.*, 2003; Gallagher *et al.*, 2008).

One way to assess the quality of drug prescriptions for elderly patients is to use instruments that incorporate explicit (Bongue *et al.*, 2009) and implicit indicators. The former list the drugs considered inappropriate for this age group and the latter consider the pathophysiology of the patient and the use of concomitant medications. However, these instruments are only tools that can guide drug prescription (Smet *et al.*, 2007; Spinewine *et al.*, 2007; Castelino *et al.*, 2009) and must not replace clinical and pharmacotherapeutic assessment for the selection of the most appropriate drug in order to obtain the best results (Castelino *et al.*, 2009).

Several criteria that evaluate the safety of pharmacotherapy for elderly people have been published, however no one criteria is established as a gold standard. Therefore, the aim of this study was to: 1) identify the instruments developed to assess the safety of pharmacotherapy for elderly people; 2) determine the drugs considered potentially inappropriate for this age group, according to the instruments identified, and 3) identify the PIM contained in the Brazilian list of essential drugs (RENAME), in order to propose safer therapeutic equivalents for elderly people.

METHODS

During February and March of 2010, a bibliographic survey was performed in Pubmed, LILACS and PAHO databases (available at http://regional.bvsalud.org/php/index.php), in order to identify the original studies that developed or used instruments to analyze the quality of drug prescriptions for elderly people (aged ≥ 65 years). The search strategy adopted the following scientific health descriptors: *"drug prescription"* AND *"aged"* OR *"elderly people"* AND *"medication errors"*, as well as the key words: "screening tool" AND "inappropriate medications". Other relevant publications were localized by a manual search, consulting the references of selected articles.

Original studies published in journals indexed in the databases consulted, which were written in the English, Portuguese or Spanish languages and developed and/or applied instruments that contained implicit or explicit indicators for quality analysis of drug prescription for elderly people were considered eligible for the present review. The exclusion criteria comprised: review manuscripts, editorials, letters, news, abstracts of conference proceedings and data from thesis and dissertations.

The articles were independently selected by two reviewers, using the techniques of floating reading and content analysis. The first allowed the pre-selection of primary studies whose titles and abstracts referred to the

theme of the study. Each pre-selected study was assessed by the technique of content analysis, in order to verify that it matched the inclusion criteria previously established and to identify the drugs considered inappropriate for use in senescence.

The drugs classified as PIM by the instruments identified were analyzed, in order to determine whether they are present in the 16th WHO Model List of Essential Medicines (WHO, 2010) and in the List of Essential Medicines in Brazil (RENAME, 2010) (Brasil, 2010). For those included in the criteria of essential medicines (PIM present in WHO and RENAME lists), safer equivalent therapies were suggested, where possible, on the basis of articles consulted and the pharmacological characteristics of the drugs.

Since the implicit criteria require clinical evaluation of patient and of the drugs taken, the instruments using these indications do not list the PIM for the elderly population, since any drug could be considered inappropriate. For this reason, they were not considered for data tabulation.

RESULTS

By the search strategy proposed, 203 articles were identified. Of these, 156 satisfied the exclusion criteria and 47 had their content analyzed. After content analysis, 12 of these articles were excluded, since they did not refer to the instruments used to evaluate the safety of pharmacotherapy for elderly people. After this process, 34 articles were considered eligible for the study.

Fifteen instruments to assess the quality of drug prescriptions for elderly people were identified: the Beers criteria (1991) (Beers *et al.*, 1991) and their updates in 1997 (Beers, M.H.; 1997), 2003 (Fick *et al.*, 2003), the *Medication Appropriateness Index* (MAI) (Hanlon *et al.*, 1992), the Lipton (Lipton *et al.*, 1993) and McLeod (McLeod *et al.*, 1997) criteria, the HEDIS method (Pugh *et al.*, 2006), *Norwegian quality indicators for prescribing* (Brekke *et al.*, 2008), *Swedish quality indicators of prescription* (Johnell, Fastbom, 2008), the *Improving Prescribing in the Elderly Tool* (Ipet) (Naugler *et al.*, 2000), the *French list of inappropriate drugs* (Laroche *et al.*, 2007), *the Norwegian list of inappropriate drugs* (Straand, Rokstad, 1999), the *Screening Tool to Alert doctors to the Right Treatment* (START) (Barry *et al.*, 2007), *Zhan criteria* (Zhan *et al.*, 2001), and the *Screening Tool of Older Persons' Potentially Inappropriate Prescriptions* (STOPP) (Gallagher, O'Mahony, 2008). In 2012, a new version of the Beers criteria (AGS, 2012) was published. Therefore, in order to update our findings, this instrument was included in our revision. Thus, we found 16 instruments.

Of these instruments, the MAI (Hanlon *et al.*, 1992) and the Lipton criteria (Lipton *et al.*, 1993) incorporate implicit indicators for the assessment of the quality of prescriptions for the elderly.

The instruments STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert doctors to the Right Treatment) (Gallagher *et al.*, 2008) list 8 therapeutic classes of potentially inappropriate medications for the elderly.

Eleven instruments (Beers *et al.*, 1991; Beers, 1997; Straand, Rokstad, 1999; Naugler *et al.*, 2000; Zhan *et al.*, 2001; Fick *et al.*, 2003; Pugh *et al.*, 2006; Laroche *et al.*, 2007; Brekke *et al.*, 2008; Johnell, Fastbom, 2008; AGS, 2012) considered 163 drugs of 25 therapeutic classes PIM for elderly people, which should be avoided, irrespective of the diagnosis or conditions of the patient (Table I). According to WHO the Anatomical Therapeutic Chemical (ATC) Classification system, 33.1% (54/163) of PIM act on the nervous system, 16.5% (27/163) on the cardiovascular system, 6.7% (11/163) on the respiratory system, 10.4% (17/163) on the musculoskeletal system, 8.6% (14/163) on the alimentary tract and metabolism, 3.7% (6/163) on genitourinary system and sex hormones, and 1.8% (3/163) on blood and hematopoietic organs, while 0.6% (1/163) are systemic hormones and 0.6% (1/163) are anti-infective. Another 18 drugs found were classified as acting on 2 or more ATC therapeutic classes, while 14 drugs were not found in this classification.

The 2012 updating of Beers criteria (AGS, 2012) covers 72.4% of all PIM identified in the assessed studies, followed by the 2003 updating of Beers criteria (Fick *et al.*, 2003) and by the list developed in France (Laroche *et al.*, 2007) (Table II).

Finally, it was observed that 19 PIM are present in the 16th WHO Model List of Essential Medicines (WHO, 2010) and 20 (5.8%) in the RENAME 2010 (Table III). Thus, these drugs are considered essential, according to the criteria of cost, safety, quality and effectiveness. Regarding the proposal of safer equivalent therapies, seven PIM classified as essential medicines in the Rename list have no safer equivalents (Table III). When we examined the PIM classified as essential drugs in the WHO list, in eight cases it was not possible to propose safer equivalent therapies for elderly people (Table III).

In 2012, there was an update of the RENAME list, which now includes 31 PIM (acetylsalicylic acid, cáscara sagrada, chlorpromazine, fluoxetine, metoclopramide, promethazine, clobazam, clonazepam, amiodarone, amitriptyline, clomipramine, propaphenone, propranolol,

TABLE I - List of potentially inappropriate medications (PIM) for the elderly that should be avoided irrespective of diagnosis or clinical condition, according to the methods identified in PAHO (available in: http://regional.bvsalud.org/php/index.php), Lilacs and Pubmed databases, during the period between February and March 2010 (n=12)

Drugs / ATC Code	Beers *et al.*, 1991	Beers, 1997	Fick *et al.*, 2003	Brekke *et al.*, 2008	Straand *et al.*, 1999	Johnell *et al.*, 2008	Pugh *et al.*, 2006	Laroche *et al.*, 2007	Zhan *et al.*, 2001	Naugler *et al.*, 2000	Beers *et al.*, 2012	Gallagher *et al.*, 2008
Ethacrynic acid (C03CC01)			X									
Analgesics												X
Salicylic acid (>325mg/d)(N02BA01)											X	
Diclofenac (M01AB05)											X	
Diflunisal (N02BG)											X	
Etodolac (M01AB08)											X	
Fenoprofen (M01AE04)											X	
Ibuprofen (M01AE01)											X	
Indometacin (M01AB01)	X	X	X		X			X	X		X	
Ketoprofen (M01AE03)											X	
Ketorolac (M01AB15)			X				X				X	
Mefenamic acid (M01AG01)											X	
Meloxicam (M01AC06)											X	
Nabumetone (M01AX01)											X	
Naproxen (M01AE02)			X								X	
Oxaprozin (M01AE12)			X								X	
Phenylbutazone (M01AA01)	X	X						X				
Piroxicam (M01AC01)			X								X	
Sulindac (M01AB02)											X	
Tolmetin (M01AB03)											X	
Antiparkinson agents												
Benzatropine (N04AC01)											X	
Trihexyphenidyl (N04AA01)											X	
Antispasmodic	X											
Belladonna alkaloids (A03BA)		X	X				X		X		X	
Clidinium-chlordiazepoxide (A033CA02)	X	X	X								X	
Dicyclomine (A03AA07)		X	X				X		X		X	
Hyoscyamine (A03BA03)		X	X				X		X		X	
Propantheline (A03AB05)		X					X		X		X	
Oxybutynin (G04BD04)		X	X			X		X	X			
Scopolamine (A04AD01)											X	
Anti-emetics												
Trimethobenzamide (none)	X	X	X				X		X			
Amphetamines and anorexic oral anti-infectives			X				X					
Nitrofurantoin (J01XE01)	X		X				X	X			X	
Anticholinergics						X					X	
Antidepressants						X						
Amitriptyline (N06AA09)	X	X	X	X	X			X	X	X	X	
Amoxapine (N06AA17)								X				
Clomipramine (N06AA04)				X				X			X	
Doxepin (N06AA12)		X	X	X				X	X	X	X	
Fluoxetine (N06AB03)			X									
Imipramine (N06AA02)								X		X	X	

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Maprotiline (N06AA21)								X				
Trimipramine (N06AA06)				X				X			X	
Oral antidiabetics												
Carbutamide (A10BB06)								X				
Chlorpropamide (A10BB02)	X	X	X	X	X		X		X		X	
Glipizide (A10BB07)								X				
Glibenclamide (A10BB01)											X	
Antihistamines						X						
Alimemazine (R06AD01)				X				X				
Brompheniramine (R06AB01)								X			X	
Carbinoxamine (R06AA08)								X			X	
Cimetidine (A02BA01)	X		X					X				
Clemastine (R06AA04)											X	
Cyproheptadine (R06AX02)		X	X				X	X	X		X	
Chlorpheniramine (R06AB02)		X	X				X		X		X	
Dexbrompheniramine(R06AB06)											X	
Dexchlorpheniramine(R06AB02)		X	X	X			X	X			X	
Diphenhydramine (R06AA02)		X	X				X		X		X	
Doxylamine (R06AA09)								X			X	
Hydroxyzine (N05BB01)		X	X	X			X	X	X		X	
Promethazine (R06AD02)		X	X	X			X	X	X		X	
Tripelennamine (R06AC04)		X	X				X					
Triprolidine (R06AX07)											X	
Antiplatelet												
Dipyridamole (B01AC07)	X	X	X		X		X	X	X		X	
Ticlopidine (B01AC05)		X	X					X	X		X	
Antipsychotics						X						
Cyamemazine (N05AA06)								X				
Chlorpromazine (N05AA01)				X				X				
Chlorprothixene (N05AF03)				X								
Fluphenazine (N05AB02)								X				
Haloperidol (N05AD01)	X			X				X				
Levomepromazine (N05AA02)				X				X				
Mesoridazine (N05AC03)			X				X				X	
Perphenazine (N05AB03)								X				
Pipotiazine (N05AC04)								X				
Prochlorperazine (N05AB04)				X								
Pericyazine (N05AC01)								X				
Thioridazine (N05AC02)	X		X				X				X	
Cardiovascular												X
Amiodarone (C01BD01)			X								X	
Clonidine (C02AC01)			X					X			X	
Digoxin (C01AA05)		X	X					X			X	

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Disopyramide (C01BA03)		X	X					X	X		X	
Dofetilide (C01BD04)											X	
Doxazosin (C02CA04)			X								X	
Dronedarone (C01BD07)											X	
Flecainide (C01BC04)											X	
Guanabenz (none)											X	
Guanadrel (none)			X				X					
Guanfacine (C02AC02)								X			X	
Guanethidine (C02CC02)			X				X					
Hydrochlorothiazide (C03AA03)	X	X										
Ibutilide (C01BD05)											X	
Methyldopa (C02AB)	X	X	X		X			X	X		X	
Moxonidine (C02AC05)								X				
Nifedipine (C08CA05)			X				X	X			X	
Nicardipine (C08CA04)								X				
Prazosin (C02CA01)											X	
Procainamide (C01BA02)											X	
Propafenone (C01BC03)											X	
Propranolol (C07AA05)	X				X							
Quinidine (C01BA01)											X	
Reserpine (C02AA02)	X	X	X					X	X		X	
Rilmenidine (C02AC06)								X				
Sotalol (C07AA07)											X	
Spironolactone (C03DA01)											X	
Terazosin (G04CA03)											X	
Ergot derivatives (C04AE)		X	X									
Descongestants												
Phenylephrine (R01AA04)	X											
Pseudoephedrine (R01BA02)	X											
Oxymetazoline (R01AA05)	X											
Hypnoanalgesics												
Meperidine (N02AB02)		X	X				X		X		X	
Pentazocine (N02AD01)	X	X	X		X		X				X	
Pethidine (N02AB02)				X								
Propoxyphene (N02AC04)	X	X	X	X	X		X		X			
Hypnotics/sedatives						X						
Barbiturates							X		X			
Amobarbital (N05CA02)											X	
Butabarbital (none)											X	
Butalbital (none)											X	
Mephobarbital (N03AA01)											X	
Pentobarbital (N05CA01)	X	X	X								X	
Phenobarbital (N03AA02)											X	

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Secobarbital (N05CA06)	X	X	X								X	
Benzodiazepines												
Long-term						X				X		
Bromazepam (N05BA08)								X				
Chlordiazepoxide (N05BA02)	X	X	X				X	X	X		X	
Clobazam (N05BA09)								X				
Clonazepam (N03AE01)											X	
Clorazepate (N05BA05)			X				X	X			X	
Diazepam (N05BA01)	X	X	X			X	X		X		X	
Flurazepam (N05CD01)	X	X	X				X				X	
Flunitrazepam (N05CD03)				X		X						
Halazepam (N05BA13)			X				X					
Loflazepate (N05BA18)								X				
Nitrazepam (N05CD02)				X		X		X				
Nordazepam (N05BA16)								X				
Quazepam (N05CD10)			X				X				X	
Prazepam (N05BA11)								X				
Tetrazepam (M03BX07)								X				
Short term												
Alprazolam (N05BA12)	X	X	X								X	
Estazolam (N05CD04)								X			X	
Eszopiclone (N05CF04)											X	
Lorazepam (N05BA06)		X	X								X	
Oxazepam (N05BA04)	X	X	X								X	
Temazepam (N05CD07)		X	X								X	
Triazolam (N05CD05)	X	X	X								X	
Zaleplon (N05CF03)											X	
Zolpidem (N05CF02)		X									X	
Meprobamate (N05BC01)	X	X	X				X				X	
Endocrine												X
Androgens (G03B)												
Methyltestosterone (G03BA02)			X				X				X	
Testosterone (G03BA03)											X	
Desiccated thyroid (H03)			X				X				X	
Estrogen (G03C)			X				X				X	
Growth hormone (L03)											X	
Insulin, sliding scale (A10AB)											X	
Megestrol (G03AC05)											X	
Gastrointestinal/ laxatives												X
Bisacodyl (A06AB02)			X					X				
Cáscara Sagrada (A06AB07)			X					X				
Metoclopramide (A03FA01)											X	
Mineral oil (A06AA)			X					X			X	

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Castor oil (A06AB05)			X					X				
Ranitidine (A02BA02)	X											
Muscle relaxants												X
Baclofen (M03BX01)								X				
Carisoprodol (M03BA02)	X	X	X	X			X		X		X	
Cyclobenzaprine (M03BX08)	X	X	X				X		X		X	
Chlorzoxazone (M03BB03)		X	X				X		X		X	
Metaxalone (none)		X	X				X		X		X	
Methocarbamol (M03BA03)	X	X	X				X	X	X		X	
Orphenadrine (M03BC01)	X		X				X				X	
Solifenacin (G04BD08)								X				
Tolterodine (G04BD07)								X				
Ferrous sulphate (B03AA07)	X	X	X									
Theophylline (R03DA04)				X								
Treatments for dementia												
Cyclandelate (C04AX01)	X	X	X				X					
Isoxsuprine (C04AA01)	X		X				X				X	

TABLE II - Frequency of drugs considered potentially inappropriate medications (PIM) for elderly people, according to the instruments identified in Paho, Lilacs and Pubmed databases in February and March 2010, whose use should be avoided irrespective of the diagnosis or conditions of the patient

Instruments	PIM - N (%)
Beers (2012)	118 (72.4)
Fick DM, *et al.* (2003)	73 (44.7)
Laroche ML, *et al.* (2007)	61 (37.4)
Beers MH, *et al.* (1997)	49 (30.0)
Pugh MJV, *et al.* (2006)	44 (26.9)
Beers MH. (1991)	38 (23.3)
Zhan C, *et al.* (2001)	33 (20.2)
Breeke M, *et al.* (2008)	19 (11.6)
Johnell K, *et al.* (2008)	10 (6.1)
Straand J, *et al.* (1999)	9 (5.5)
Naugler CT, *et al.* (2000)	4 (2.4)
Total of PIM	163 (100.0%)

ranitidine, spironolactone, estrogens, diazepam, digoxin, phenobarbital, haloperidol, hydrochlorothiazide, ibuprofen, insulin, dexchlorpheniramine, nifedipine, nitrofurantoin, doxazosin, methyldopa, mineral oil, ferrous sulphate, trihexyphenidyl). In this update, the only PIM that was removed from the list was testosterone. However, testosterone was maintained in the 17th WHO Model List of Essential Medicines.

Moreover, among the 16 criteria identified, only eleven listed the drugs that should be avoided on the basis of diagnosis or the conditions of patient (drug interaction with the disease), the co-prescriptions that should be avoided in senescence and drugs for which is necessary to pay attention to the dose, duration and frequency of the treatment (Table III).

DISCUSSION

The pharmacotherapy prescribed, especially for the elderly population, should be effective and avoid potentially harmful drugs, since most of the adverse drug events appear in the post-commercialization period. Topinková *et al.* (2012) showed that strategies have been developed to target these goals which are focused on drug

TABLE III - Potentially inappropriate medications (PIM) for elderly people listed by the instruments identified in Paho, Lilacs and Pubmed databases, during Februrary and March 2010, which are present in the Brazilian list of essential medicines (RENAME 2010) and in the 16th WHO Model List of Essential Drugs, and their possible equivalent therapies.

RENAME 2010			WHO MODEL LIST		
PIM	Therapeutic equivalent proposed	The therapeutic equivalent is listed in Rename 2010?	PIM	Therapeutic equivalent	The therapeutic equivalent is in WHO model list?
amiodarone	verapamil	yes	amidarone	verapamil	yes
amitriptyline	sertraline	no	amitriptilyne	sertraline	no
clomipramine	sertraline	no	clorfenidramina	loratadine	no
clonazepam	* short-acting benzodiazepine	no	clomipramine	sertraline	no
chlorpromazine	quetiapine	yes	chlorpromazine	quetiapine	no
diazepam	* short-acting benzodiazepine	no	diazepam	* short-acting benzodiazepine	yes
digoxin	-	-	digoxin	-	-
dexclorfenidramine	loratadine	yes	fluoxetine	sertraline	no
estrogen	-	-	haloperidol		-
fluoxetine	sertraline	no	hydrochlorothiazide	-	-
haloperidol	-	-	lorazepam	-	
hydrochlorothiazide	-	-	methyldopa	losartan	no
methyldopa	losartan	yes	nifedipine	-	yes
ciprionate testosterone	-	-	nitrofurantoin	ciprofloxacin	yes
nifedipine	-	yes	promethazine	loratadine	no
nitrofurantoin	ciprofloxacin	yes	propranolol	-	-
promethazine	loratadine	yes	ranitidine	omeprazole	yes
propranolol	atenolol	yes	ferrous sulphate	-	-
ranitidine	omeprazole	yes	testosterone	-	-
ferrous sulphate	-	-			

*The dose in the elderly should be half or less than half the dose recommended for a young adult <27>.

appropriateness, adherence and adverse drug events. The authors highlight the medication review as one of the more promising interventions to assess the risk/benefit of geriatric pharmacotherapy. To promote this kind of safety assessment, our study identified the instruments that may be applied to assess the quality of medical prescription for elderly people.

However, since the criteria were developed in North America (Beers criteria and their updates) and Europe, there is a need to adapt an instrument of PIM classification to Brazilian conditions (Ribeiro *et al.*, 2005), since 23% (38/165) of inappropriate geriatric medicines are not marketed in Brazil (ethacrynic acid, alimemazine, amobarbital, amoxapine, butalbital, carbutamide, cyamemazine, cyclandelate, clidinium-chlordiazepoxide, chlorprothixen, diflunisal, eszopiclone, guanabenz, guanadrel, guanfacine, guanethidine, halazepam, loflazepate, meprobamate, mesoridazine, metaxalone, methocarbamol, nicardipine, nordazepam, oxaprozin, pentazocine, perphenazine, prazepam, procainamide, prochlorperazine, propantheline, quazepam, secobarbital, temazepam, tetrazepam, tolmetin, trimethobenzamide, trimipramine). A review carried out by Corsonello *et al.* (2012) corroborates this argument. The authors noted that the START/STOPP criteria were developed to promote the prevention of inappropriate prescribing in European nations, since the 2003 updated Beers criteria include drugs that are not available in Europe or hardly ever are prescribed. Therefore, with the aid of Brazilian criteria, the prevalence of appropriate pharmacotherapy may be

TABLE IV - List of potentially inappropriate medications (PIM) for the elderly that should be avoided as indicated by the clinical diagnosis of the patient (drug interaction with disease), the dose, frequency and duration of the drug administration and drug association, according to the methods identified in PAHO (available at: http://regional.bvsalud.org/php/index.php), Lilacs and Pubmed databases, during the period between February and March 2010 (n=10)

Drugs	Beers *et al.*, 1991	Beers, 1997	Fick *et al.*, 2003	McLeod *et al.*, 1997	Straand *et al.*, 1999	Gallagher, O'Mahony, 2008	Naugler *et al.*, 2000	Laroche *et al.*, 2007	Brekke *et al.*, 2008	Beers *et al.*, 2012
Combinations										
NSAIDs + Diuretics									X	
NSAIDS + Meperidine ou Pentazocine				X						
NSAIDS + Piroxicam, Ketorola or Mefenamic acid				X						
NSAIDS + ACEi									X	
NSAIDS + SSRI									X	
NSAIDS + Warfarin				X		X			X	
Amitriptyline + Chlordiazepoxide		X	X							**X**
Amitriptyline + Perphenazine	**X**	**X**	**X**							**X**
Anticholinergic + Antipsychotics				X			X			
Cimetidine + Warfarin				X						
Clidinium + Chlordiazepoxide			X							**X**
Corazepato + Acepromazine								X		
Desclorfeniramina + Betamethasone								X		
SSRI + MAOI				X						
Methyldopa + Hydrochlorothiazide		X	X							
Dose limits, frequency and duration of treatment										
Acetylsalicylic acid ≥150mg/dia (dose)						X				
Pain relievers containing codeine					X					
Antibiotics prescribed for the first crisis of bronchitis					X					
Gastrointestinal antispasmodics					X					
1st generation antihistamines (duration)						X				
Antipsychotic drugs (dose, duration)	**X**				X					
Antipsychotics for nonpsychotic diagnoses					X					
Barbiturates (duration)				X						
Benzodiazepines (dose, duration)	**X**			X	X	X				
H2 blockers (dose. frequency and duration)	**X**									
Decongestants (duration)	**X**									
Digoxin (dose)	**X**									
Iron supplements (dose and frequency)	**X**									
Thiazides (dose)	**X**				X					
Three or more psychotropic drugs (duration)									X	
Interaction Pathology										
Adenoma of the prostate, glaucoma and urinary retention X anticholinergic								X		
Angina in patients with a history of asthma, COPD or heart failure X β-blockers				X						
Anorexia and malnutrition X central nervous system stimulants			X							
Conductive cardiac abnormalities X tricyclic antidepressant						X				
Arrhythmias X tricyclic antidepressants			X							
No history of coronary symptoms, cerebral or peripheral vascular occlusive or event X Acetylsalicylic acid						X				

TABLE IV - List of potentially inappropriate medications (PIM) for the elderly that should be avoided as indicated by the clinical diagnosis of the patient (drug interaction with disease), the dose, frequency and duration of the drug administration and drug association, according to the methods identified in PAHO (available at: http://regional.bvsalud.org/php/index.php), Lilacs and Pubmed databases, during the period between February and March 2010 (n=9) (cont.)

Drugs	Beers *et al.*, 1991	Beers, 1997	Fick *et al.*, 2003	McLeod *et al.*, 1997	Straand *et al.*, 1999	Gallagher, O'Mahony, 2008	Naugler *et al.*, 2000	Laroche *et al.*, 2007	Brekke *et al.*, 2008	Beers *et al.*, 2012
Chronic constipation without concomitant use of laxatives X opioids for more than 2 weeks						X				
Constipation X tricyclic antidepressant						X				
Seizures X clozapine, chlorpromazine, thioridazine and thiothixene			X							
Dementia X anticholinergics, trihexafenidil, tropatepina, biperiden, neuroleptics (except risperidone and olanzapine) and benzodiazepines								X		
Depression X active metabolites with tricyclic antidepressant (eg amitriptyline or imipramine)				X						
Depression X long-acting benzodiazepines and sympatholytic agents			X							
Depression X methylphenidate				X			X			
Clotting disorders X NSAIDs, dipyridamole, ticlopidine and clopidogrel			X							
Diabetes mellitus and frequent hypoglycemia X β-blockers						X				
Diabetes X corticoids				X						
Diarrhea or gastroenteritis of unknown cause severe X diphenoxylate, loperamide or codeine				X		X	X			
Parkinson's Disease X Metoclopramide, conventional antipsychotics, tacrine			X							
Raynaud's DiseaseX prolonged use of β-adrenergic blocker				X						
Moderate pain X long-term use of potent opioids as a first treatment option						X				
COPD X beta blockers and benzodiazepines long-term			X	X		X	X			
COPD X theophylline						X				
Muscle spasms X cyclobenzaprine or methocarbamol				X						
Stress X benzodiazepínios beta-blockers and long acting			X							
Atrial fibrillation X disopyramide				X						
Drop X thiazide diuretic				X		X	X			
Drop X indomethacin				X						
Benign prostatic hyperplasia, glaucoma or cardiac arrest X tricyclic antidepressant				X			X			
Moderate to severe hypertension X NSAIDS				X		X	X			
Hypertension X phenylpropanolamine, pseudoephedrine and amphetamines			X							
Hypertension X reserpine				X						
Postural hypotension X tricyclic antidepressants				X						
Postural hypotension X chlorpromazine				X						
Urinary incontinence X urapidil and prazosin								X		
Insomnia X decongestants, theophylline, methylphenidate, MAOI, amphetamine			X							

TABLE IV - List of potentially inappropriate medications (PIM) for the elderly that should be avoided as indicated by the clinical diagnosis of the patient (drug interaction with disease), the dose, frequency and duration of the drug administration and drug association, according to the methods identified in PAHO (available at: http://regional.bvsalud.org/php/index.php), Lilacs and Pubmed databases, during the period between February and March 2010 (n=9) (cont.)

Drugs	Beers *et al.*, 1991	Beers, 1997	Fick *et al.*, 2003	McLeod *et al.*, 1997	Straand *et al.*, 1999	Gallagher, O'Mahony, 2008	Naugler *et al.*, 2000	Laroche *et al.*, 2007	Brekke *et al.*, 2008	Beers *et al.*, 2012
Insomnia X prolonged use of triazolam				X						
Heart failure X NSAIDS				X		X				
Heart failure X β-adrenergic blocker				X			X			
Heart failure X Calcium channel blockers				X		X	X			
Heart failure X drugscom disopyramide and high sodium			X	X						
Chronic renal failure X NSAIDS				X		X				
Obesity X olanzapine			X							
Chronic constipation X calcium channel blockers, anticholinergics, and tricyclic antidepressants			X			X				
Chronic osteoarthritis X phenylbutazone				X						
Moderate osteoarthritis X NSAIDS				X		X	X			
Osteoarthritis or rheumatoid arthritis X long-term corticosteroids						X				
Parkinson X long-term neuroleptic						X				
Cognitive impairment X anticholinergic or antispasmodic				X						
Cognitive impairment X tricyclic antidepressant						X				
Cognitive impairment X antimuscarinic						X				
Cognitive impairment X barbiturates, anticholinergics, antispasmodics, muscle relaxants and CNS stimulants			X							
Cognitive impairment X niacin or pentoxifylline				X						
Cognitive impairment X Prolonged use of opioids						X				
Renal damage X digoxin > 0,125 mg/dia						X				
Prevention of myocardial X dipyridamole				X		X				
Chronic prostatism X antimuscarinic						X				
Prostatism or history of urinary retention X tricyclic antidepressant						X				
Urinary retention X anticholinergics, antihistamines, GI antispasmodics, muscle relaxants, oxybutynin, flavoxate, antidepressants, and tolterodine			X							
Syncope or falls X short-acting benzodiazepines or tricyclic antidepressants or intermediate			X							
Syndrome of inappropriate secretion of the hormone antidiuretic / hyponatremia X SSRI			X							
Tendency to fall X benzodiazepines, neuroleptics, vasodilators and long-term opioid						X				
Maintenance therapy of moderate to severe COPD X corticoids						X				
Dizziness X bupropion			X							
Treatment of gout when there is no contraindication to allopurinol X prolonged use of NSAIDS or colchicine						X				
Peptic ulcer without H2 antagonist or proton pump inhibitor X acetylsalicylic acid						X				
Peptic ulcer X proton pump inhibitor in the highest therapeutic dose for more than 8 weeks						X				

TABLE IV - List of potentially inappropriate medications (PIM) for the elderly that should be avoided as indicated by the clinical diagnosis of the patient (drug interaction with disease), the dose, frequency and duration of the drug administration and drug association, according to the methods identified in PAHO (available at: http://regional.bvsalud.org/php/index.php), Lilacs and Pubmed databases, during the period between February and March 2010 (n=9) (cont.)

Drugs	Beers *et al.*, 1991	Beers, 1997	Fick *et al.*, 2003	McLeod *et al.*, 1997	Straand *et al.*, 1999	Gallagher, O'Mahony, 2008	Naugler *et al.*, 2000	Laroche *et al.*, 2007	Brekke *et al.*, 2008	Beers *et al.*, 2012
UlcerX NSAIDS			X	X		X	X			
Questionable efficacy										
Benzodiazepines							X			
Drugs that act in the gastrointestinal tract with anticholinergic properties							X			
Cerebral vasodilator							X			

NSAIDs: nonsteroidal anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease; ACEI: angiotensin-converting-enzyme inhibitor; MAOI: monoamino oxidase inhibitor; SSRI: selective serotonin reuptake inhibitor; CNS: central nervous system.

robustly assessed, allowing interventions to decrease medication prescribing errors.

Furthermore, the inclusion of safer equivalent therapies for the elderly in the list of Brazilian essential medicines may be another approach able to promote the safe use of drugs for the elderly, as well as to increase their access to less harmful medicines. This measure could have a great impact in developing countries, where most of the population is attended in public health care services, which commonly use RENAME to standardize their drugs. In Brazil, the total coverage of the public health service is 70% (IBGE, 2009) and approximately 20% of PIM are essential medicines (RENAME 2012). Although they meet the criteria of quality, safety, effectiveness and low cost for the majority of population, they are considered unsafe for elderly people. Therefore, the RENAME should make an assessment of the cost/benefit of the inclusion of safer alternatives for this age group, presented as a safety indicator of Pharmaceutical Assistance Management.

It is important to mention that there is no safer equivalent therapies for seven of the PIM considered essential medicines. In these cases, the development of clinical protocols clarifying the conditions of use and the measures required to avoid harming the health is essential. In addition pharmacotherapeutic follow-up may optimize the treatment, since it allows early recognition of negative clinical outcomes and may avoid therapeutic failure by noncompliance (Maust *et al.*, 2013).

Finally, particular care should be taken with PIM that are over the counter (OTC) drugs (salicylic acid, ibuprofen, naproxen, belladonna alkaloids, scopolamine, dexchlorpheniramine, doxylamine, bisacodyl, cáscara sagrada, mineral oil, castor oil, ferrous sulphate, brompheniramine, carbinoxamine, cyproheptadine, chlorpheniramine, phenylephrine, carisoprodol, orphenadrine). This fact highlights the role of pharmacists in providing quality information regarding the correct use of drugs. Recently, the Brazilian Pharmacy Federal Council approved the pharmaceutical prescribing of OTC drugs (CFF, 2013), so that the treatment of minor disorders in drugstores is feasible. In this setting, the pharmacist should consider the risk/benefit of using a drug, the clinical conditions of the patient (renal or hepatic impairments, allergies, morbidities and comorbidities that contraindicate its use) and the safety of the drug to choose the best option for the user. Therefore, it is important aware them regarding the sanitary risk involving the use of PIM by elderly people.

Study limitations

The data may be underestimated because of selection bias, due to: 1) the search strategy in the databases; 2) data collection period; 3) restriction os search to; 4) articles selected for analysis being written in Spanish, English and Portuguese languages alone, and 5) 26 [12.8% (26/203)] manuscripts being unavailable for analysis. Therefore, some other criteria developed to assess the quality of drugs prescribed for elderly people may not have been identified by the methods used in this study.

CONCLUSION

The Brazilian register of essential medicines (RENAME) lists effective, safe and economic drugs.

However, approximately 25% of them are considered potentially inappropriate for elderly people. Therefore, they do not meet the safety attribute for this age group, most of whom are attended in public health care services and, in general, use polypharmacy. Thus, it is necessary for less noxious drugs for this population to be included in RENAME, in order to provide access to more effective treatments with less harmful potential. In this setting, the pharmacist can contribute to the safety assessment and follow-up of geriatric pharmacotherapy, mainly for those PIM that have no safer equivalent therapies (digoxin, estrogen, haloperidol, hydrochlorthiazide, ciprionate testosterone, nifedipine and ferrous sulphate), as well as for those that are OTC drugs whose use is not exempt from counseling. These measures would meet the national policy of risk management. Furthermore, the intensive monitoring of medicines allows the establishment of safety indicators for Pharmaceutical Assistance.

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